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(54) Title: USE OF HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY PAIN

(57) Abstract

Azacyclic and heterocyclic derivatives having kappa agonist activity are useful in the treatment of inflammatory pain.

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USE OF HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY PAIN

The present invention relates to the use of certain compounds for the manufacture of medicaments for the treatment of inflammatory pain; to a method of treatment of inflammatory pain; and to pharmaceutical compositions for the treatment of such pain.

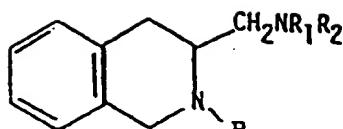
EP-A-228246, 232612, 232989, 260041, 261842, 275696, 330360, 10 333315, 333427, 361791, 370732, 409489, WO 91/08205, WO 91/08206, WO 91/17116 and WO 91/17981 (all Dr. Lo. Zambeletti S.p.a.) describe classes of heterocyclic derivatives which exhibit kappa receptor agonism and are of potential therapeutic utility as analgesics.

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It has now been found that compounds of these classes activate peripheral kappa opioid receptors located on sensory nerve terminals. Activation of such receptors can lead to a reduction in the release of neurogenic 20 inflammatory mediators released from the nerve terminals and to a reduction in transmission of nociceptive information to the CNS. Compounds of the present invention are, therefore, of potential use as peripheral analgesics in the treatment of a range of inflammatory painful conditions - such as 25 arthritis and low back pain - since they may reduce both the causes and consequences of local inflammation.

According to the present invention there is provided the use of a compound, or a pharmaceutically acceptable salt or 30 solvate thereof, for the manufacture of a medicament for the treatment of inflammation pain, wherein the compound is selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV) or (XVI):

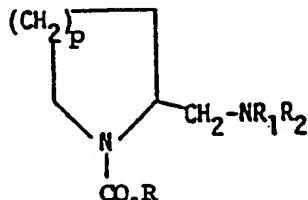
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(I)

in which R is an acyl group containing a substituted or
 10 unsubstituted carbocyclic or heterocyclic aromatic ring and
 R₁ and R₂ are independently C₁₋₆ alkyl groups or together
 form a C₃₋₆ polymethylene or alkenylene group;

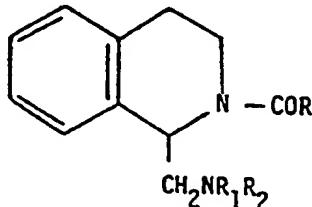
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(II)

20 in which R, R₁ and R₂ are as defined for formula (I), and p
 is 1, 2, 3 or 4;

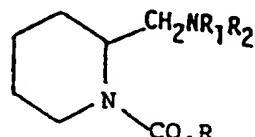
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(III)

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(IV)

in which R is a group:

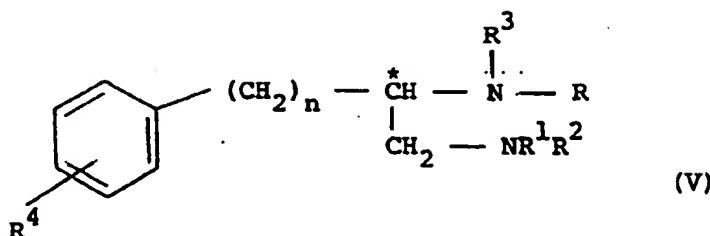
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in which R3 is Br, NO2 or CF3; and R1 and R2 are as defined in formula (I);

10

15



in which R is as defined in formula (I);

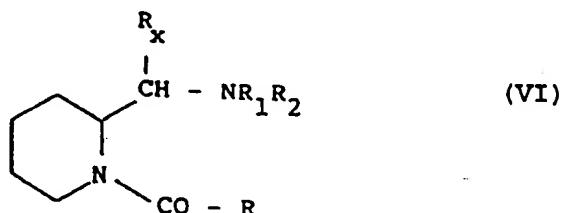
20 R¹ and R² each independently represents an alkyl, alkenyl or alkynyl group or R¹ together with R² represents a C₃₋₆ polymethylene or alkenylene group;

R³ represents hydrogen or alkyl;

25 R⁴ represents hydrogen, halogen, alkyl, hydroxy, alkoxy, nitrile, nitro, amino or mono or disubstituted amino; and

n represents 0 or 1;

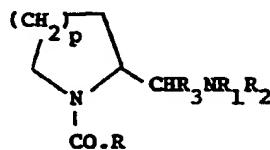
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in which R is as defined in formula (I);
 R₁ and R₂ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₄₋₆ cycloalkyl or C₄₋₁₂ cycloalkylalkyl or
 5 together form a C₂₋₆ polymethylene or C₂₋₆ alkenylene group,
 optionally substituted with a hetero-atom, provided that R₁
 and R₂ are not simultaneously hydrogen;
 Rx is C₁₋₆ alkyl or phenyl, or Rx together with R₁ form a
 - (CH₂)₃- or - (CH₂)₄- group;

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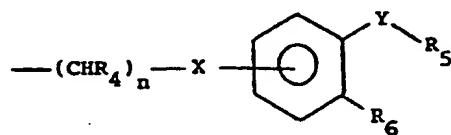
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(VII)

in which R₁ and R₂ are independently hydrogen, C₁₋₆ alkyl,
 C₂₋₆ alkenyl, C₃₋₆ cycloalkyl or C₄₋₁₂ cycloalkylalkyl
 20 groups, or together form a C₂₋₈ branched or linear
 polymethylene or C₂₋₆ alkenylene group optionally
 substituted with a hetero-atom, provided that R₁ and R₂ are
 not simultaneously hydrogen;
 R₃ is hydrogen, C₁₋₆ alkyl, or phenyl, or R₃ together with
 25 R₁ form a - (CH₂)₃- or - (CH₂)₄- group;
 p is 1, 2, 3 or 4, and
 R is a group of formula

30



in which the group $-(CH_4)_n-X-$ is in the meta- or para-position with respect to YR_5 or R_6 , R_4 is hydrogen or C_{1-6} alkyl;

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n is 0, 1 or 2;

X is a direct bond, or O, S or NR_a in which R_a is hydrogen or C_{1-6} alkyl;

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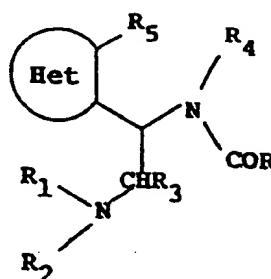
Y is $>C=O$, $>CHOH$, $>S=O$ or $>SO_2$;
each of R_5 and R_6 is C_{1-6} alkyl, or

R_5 and R_6 are linked together and R_5 represents $-(Z)_m-$ where 15 m is 0 or 1 and Z is O, S or NR_7 where R_7 is hydrogen or C_{1-6} alkyl;

and R_6 represents $-(CH_2)_q-$ where q is an integer of from 1 to 4, and in which one or more of the $-(CH_2)-$ groups is optionally substituted by a C_{1-6} alkyl group;

20

25



(VIII)

in which R is as defined in formula (I)

30 R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a heteroatom;

R₃ is hydrogen, C₁₋₆ alkyl, or phenyl or R₃ together with R₁ form a -(CH₂)₃- or -(CH₂)₄- group;

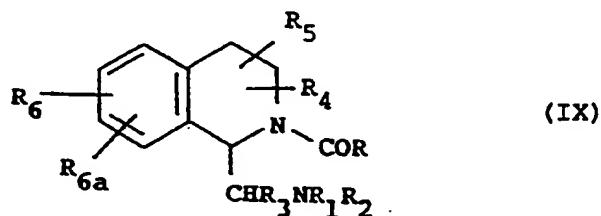
R₄ is C₁₋₆ alkyl, or phenyl;

R₅ is hydrogen or together with R₄ forms a -(CH₂)_n- group in which n = 1, 2 or 3; and

'Het' is an optionally substituted single or fused ring heterocyclic group, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur;

10

15



in which R is as defined in formula (I) and R₁ and R₂ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆

20 cycloalkyl or C₄₋₁₂ cycloalkylalkyl groups or together form a C₂₋₈ branched or linear polymethylene or C₂₋₆ alkenylene group optionally substituted with a hetero-atom;

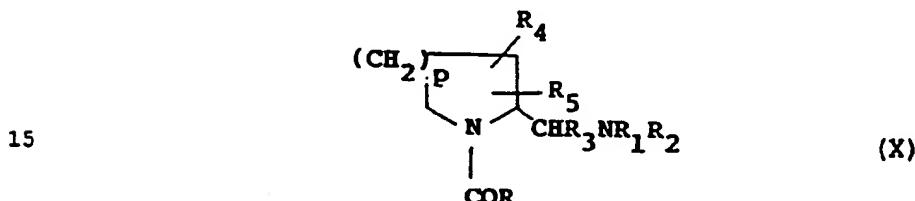
R₃ is hydrogen, C₁₋₆ alkyl, or phenyl or R₃ together with R₁ forms a -(CH₂)₃- or -(CH₂)₄-, group;

25 R₄ and R₅, which may be the same or different and may be attached to the same or different carbon atoms of the isoquinoline nucleus, are each hydrogen, halogen, hydroxy, C₁₋₆ alkyl, aryl, or R₄ together with R₅ form a -(CH₂)_p group, where p is an integer of from 1 to 5 and one or more 30 of the -(CH₂)- moieties is optionally substituted by a C₁₋₆ alkyl group.

R_6 and R_{6a} , which may be the same or different, are each hydrogen, C_{1-6} alkyl, $-CH_2OR_{6b}$, halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxy carbonyl, thiol, C_{1-6} alkylthio,

5 $\begin{array}{c} 0 \\ || \\ -O-C-R_{6c}, -NHCOR_{6d}, -NHSO_2R_{6e}, -CH_2SO_2NR_{6f}R_{6g}, \end{array}$ in which each of R_{6b} to R_{6g} is independently hydrogen, C_{1-6} alkyl, aryl or aralkyl;

10 with the proviso that R_4 , R_5 , R_6 and R_{6a} are not simultaneously hydrogen;



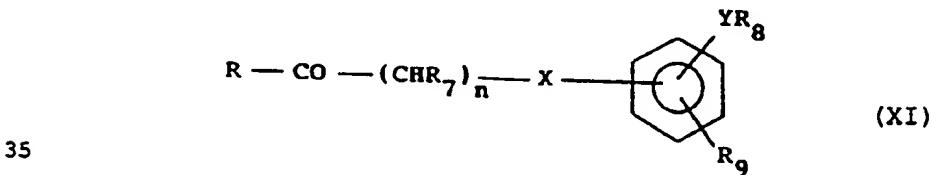
in which R is as defined in formula (I);

20 R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a hetero-atom;

25 R_3 is hydrogen, C_{1-6} alkyl or phenyl, or R_3 together with R_1 form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

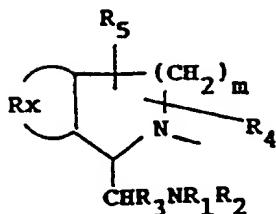
R_4 and R_5 are independently hydrogen, hydroxyl, halogen, C_{1-6} alkyl or aryl, provided both R_4 and R_5 are not simultaneously hydrogen: and p is an integer from 1 to 4;

30



in which R represents a group of formula

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in which Rx is the remainder of a heterocyclic group, or an optionally substituted phenyl group;

R₁ and R₂ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkyl or C₄₋₁₂ cycloalkylalkyl groups, or 15 together form a C₂₋₈ branched or linear polymethylene or C₂₋₆ alkenylene group, optionally substituted with a hetero-atom;

R₃ is hydrogen, C₁₋₆ alkyl, or phenyl, or R₃ together with R₁ form a -(CH₂)₃- or -(CH₂)₄- group;

20 R₄ and R₅, which may be located on the same or different carbon atoms, are independently hydrogen, C₁₋₆ alkyl, or phenyl;

m is 1, 2 or 3;

R₇ is hydrogen or C₁₋₆ alkyl;

25 n is 0, 1 and 2;

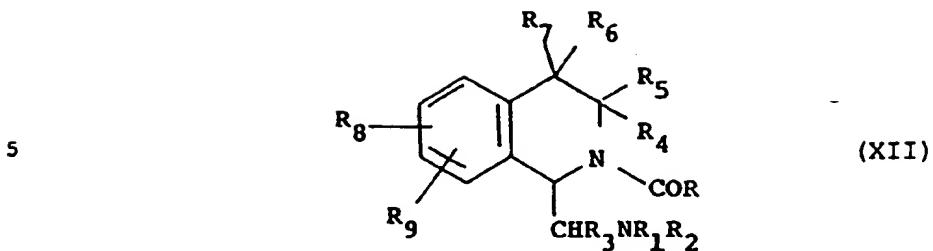
X is direct bond, or O, S or NR₆ is hydrogen or C₁₋₆ alkyl;

Y is >C=O, >CHOH, >S=O or >SO₂;

each of R₈ and R₉ is C₁₋₆ alkyl, or

30 R₈ and R₉ are linked together and R₈ represents -(Z)_p- where p is 0 or 1 and Z is O, S or NR_z where R_z is hydrogen or C₁₋₆ alkyl;

and R₉ represents -(CH₂)_q- where q is an integer of from 1 to 4;



in which R is as defined in formula (I) and R₁ and R₂ are
 10 independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkyl or C₄₋₁₂ cycloalkylalkyl groups or together form a C₂₋₈ branched or linear polymethylene or C₂₋₆ alkenylene group optionally substituted with a hetero-atom;

15 R₃ is hydrogen, C₁₋₆ alkyl, or phenyl, or R₃ together with R₁ forms a -(CH₂)₃- or -(CH₂)₄ group;
 R₄ and R₅ are identical and are hydrogen or C₁₋₆ alkyl, or together form a C₂₋₅ linear polymethylene group;
 R₆ and R₇ are identical and are hydrogen or C₁₋₆ alkyl, or
 20 together form a C₂₋₅ linear polymethylene group;
 or R₅ and R₆ are together -CH₂- when each of R₄ and R₇ is hydrogen or C₁₋₆ alkyl;
 with the proviso that R₄, R₅, R₆ and R₇ are not simultaneously hydrogen;

25

R₈ and R₉, which may be the same or different, are each hydrogen, C₁₋₆ alkyl, -CH₂OR₁₀, halogen, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, thiol, C₁₋₆ alkylthio,
 30 -OCR₁₁, -NHCOR₁₂, -NHSO₂R₁₃, -CH₂SO₂NR₁₄R₁₅, in which each of R₁₀ to R₁₅ is independently hydrogen, C₁₋₆ alkyl, aryl or aralkyl;

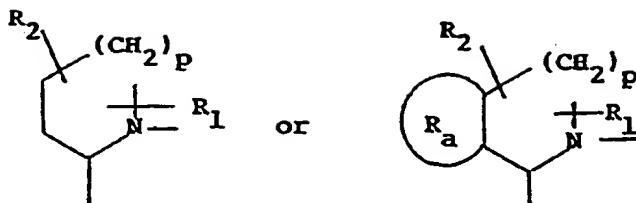
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in which:

(A) is

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10 p is 1, 2 or 3;

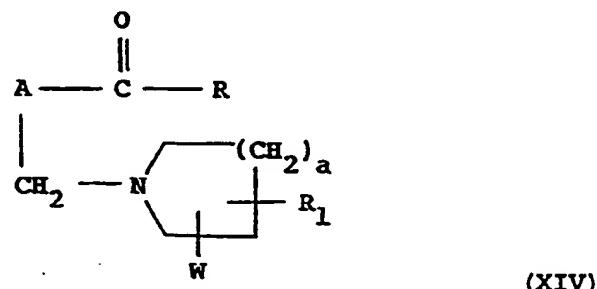
ROC- is an acyl group linked to the nitrogen atom of group (A) in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

15

R₁ and R₂ are substituents on the same or different carbon atoms and are independently hydrogen or C₁₋₆ alkyl;

20 R_a is a fused substituted or unsubstituted heterocyclic or carbocyclic aromatic ring;

25



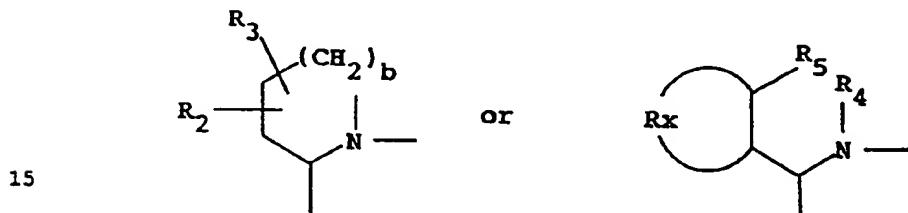
(XIV)

30 in which W, which may be attached to the same or different carbon atom as R₁, is hydroxy, C₁₋₆ alkoxy (preferably methoxy), halogen (preferably fluorine), thiol, C₁₋₆

alkylthio, hydroxy C_{1-6} alkyl, methylidene, hydroxycarbonyl, aminocarbonyl, C_{1-3} alkoxy carbonyl, NHR_{1a} or $NHCOR_{1a}$ where R_{1a} is H or C_{1-6} alkyl;

5 R_1 is hydrogen, halogen (preferably fluorine), C_{1-6} alkyl (preferably methyl) or together with W forms a keto-group or a cyclic ether or thioether containing from 1 to 4 carbon atoms;

10 A represents



in which each of R_2 and R_3 , which may be attached to the same or different carbon atom, is hydrogen, C_{1-6} alkyl, hydroxy, thiol, C_{1-6} alkoxy, C_{1-6} alkylthio or halogen (preferably fluorine);

20 R_4 is C_{1-6} alkyl;

R_5 is hydrogen or together with R_4 forms a $-(CH_2)_c-$ group optionally substituted by one or two C_{1-6} alkyl groups and attached to the same or different carbon atom;

25 R_x is the remainder of an optionally substituted single or fused ring heterocyclic group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur;

30 or R_x is the remainder of an optionally substituted phenyl group;

a is 1 or 2, b is 1, 2 or 3; c is 1, 2 or 3;

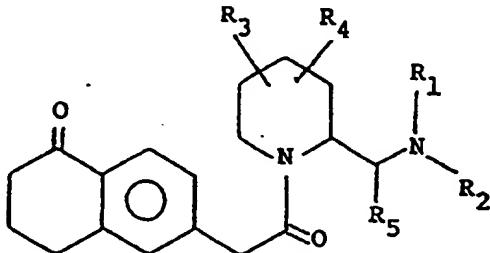
and RCO, which is linked to the nitrogen atom of the group A, is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or 5 heterocyclic aromatic ring,

with the provisos that:

- i) When A represents, , R represents a tetralone moiety, or W is halogen or C₁₋₆ alkoxy, or R₁ is other than hydrogen or a keto group with W;
- ii) When R₂ is C₁₋₆ alkyl, R₃ is other than hydrogen;
- iii) When R_x, R₄ and R₅ together form an unsubstituted tetrahydroisoquinoline group, R represents a tetralone moiety or R₁ is other than hydrogen or a keto group with W, or W is halogen or C₁₋₆ alkoxy;
- iv) When R_x, R₄ and R₅ together form a substituted tetrahydroisoquinoline group, substitution only occurs in the -(CH₂)_c- group formed by R₄ and R₅;

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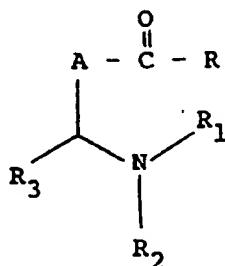
(XV)

30 in which:

R₁ and R₂ are each linear or branched C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₄₋₆ cycloalkylalkyl, C₃₋₄ alkenyl, C₃₋₆ cycloalkenyl or C₃₋₄ alkynyl,
 R₃ and R₄ are identical, and each is hydrogen or C₁₋₄ alkyl;
 5 and

R₅ is hydrogen or C₁₋₃ alkyl;

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(XVI)

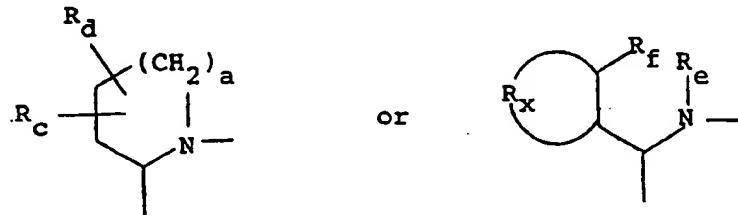
in which:

each of R₁ and R₂, which may be the same or different, is C₁₋₆ alkyl with at least one of them being substituted by at least one of halogen, (preferably fluorine or chlorine),
 20 hydroxy, C₁₋₆ alkoxy (preferably methoxy), acyloxy (preferably acetoxy), thiol, C₁₋₆ alkylthio (preferably methylthio), acylthio (preferably acetylthio) halo-C₁₋₆ alkoxy (preferably fluoro-alkoxy), COR_h, COOR_h, CONHR_h or NCHOR_h where R_h is hydrogen or C₁₋₆ alkyl, preferably methyl
 25 or ethyl;

R₃ is hydrogen or C₁₋₃ alkyl, preferably methyl;

A represents

30



in which each of R_C and R_D , which may be attached to the same or different carbon atom, is hydrogen, C_{1-6} alkyl, hydroxy, thiol, C_{1-6} alkoxy, C_{1-6} alkylthio or halogen 5 (preferably fluorine);
 R_E is C_{1-6} alkyl;
 R_F is hydrogen or together with R_E forms a $-(CH_2)_b-$ group optionally substituted by one or two C_{1-6} alkyl groups and attached to the same or different carbon atom;
10 R_X is the remainder of an optionally substituted single or fused ring heterocyclic group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur; or R_X is the remainder of an 15 optionally substituted or unsubstituted phenyl group;

a is 1, 2 or 3; b is 1, 2 or 3;

and RCO , which is linked to the nitrogen atom of the group 20 A , is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring.

In a further aspect of the invention there is provided a 25 pharmaceutical composition for use in the treatment of inflammation pain in mammals which comprises a compound of formulae (I) to (XVI) (as hereinbefore defined) or a pharmaceutically acceptable salt or solvate thereof, (hereinafter referred to as the Compound) and a 30 pharmaceutically acceptable carrier.

The invention further provides a method for the treatment and/or prophylaxis of inflammation pain in mammals, particularly humans, which comprises administering to the 35 mammal in need of such treatment and/or prophylaxis an effective amount of the Compound.

The Compound is in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 10 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the Compound.

One preferred pharmaceutically acceptable form is the 15 crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

20 Examples of the Compound in the form of a pharmaceutically acceptable salt include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, 25 benzoic, ascorbic and methanesulphonic.

An example of the Compound in the form of a pharmaceutically acceptable solvate includes a hydrate.

30 The Compounds have at least one asymmetric centre and therefore exist in more than one stereoisomeric form. The invention extends to the use of all such forms and to mixtures thereof, including racemates.

The Compounds may be prepared as described in the aforementioned documents, EP-A-228246, 232612, 232989, 260041, 261842, 275696, 330360, 333315, 333427, 361791, 5 370732, 409489, WO 91/08205, WO 91/08206, WO 91/17116 and WO 91/17981 (the subject matter of which is incorporated herein by reference) or by analogous methods thereto.

Medicaments and compositions containing the Compounds may be 10 prepared by admixture of a Compound with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

15 These conventional excipients may be employed for example as in the preparation of compositions of known agents for the treatment of inflammation pain.

Preferably, a medicament or pharmaceutical composition of 20 the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as a an agent for the treatment of inflammation pain.

25

The suitable dosage range for a Compound depends on the Compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of 30 administration.

The Compound may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single

dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

5

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

10

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if

desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or 5 may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, 10 carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of 15 glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

20 The Compounds may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example, for rectal administration as a suppository or for topical administration as a cream or lotion. They may also be 25 formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic 30 agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable 35 injection devices or in multi- dose forms such as a bottle

from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

5 The effective dose of Compound depends on the particular Compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 10 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20mg of active ingredient 15 and be administered in multiples, if desired, to give the preceding daily dose.

Within the above indicated dosage range, no adverse toxicological effect are observed with the Compounds in 20 tests which are indicative of compounds of potential use in treating inflammation pain.

The effects of the Compounds in protecting against inflammation pain may be demonstrated using the paw pressure 25 test in the monoarthritic rat as described in Eur. J. Pharm. 155, 255-264, 1988.

Following subcutaneous administration, the Compounds produce an enhanced analgesic effect in the inflamed paw compared to 30 the non-inflamed paw. The analgesic effect in the inflamed paw is completely reversed by a low intraplantar dose of the opioid antagonist, naloxone, but not by a similar dose of naloxone administered subcutaneously.

Examples of preferred Compounds are:

4-(pyrrolidin-1-yl)methyl-5-(3,4-dichlorophenyl) acetyl-

4,5,6,7-tetrahydroimidazo [4,5-c] pyridine

5 (Example 23 of EP-A-333427);

(2)-1-(4-trifluoromethyl phenylacetyl)-2-(1-pyrrolidinyl methyl) piperidine

(Example 3 of EP-A-260 041);

and

10 (2S)-1-[1-oxo-3,4,-dihydro-(2H)-naphth-6-yl]acetyl-2-

dimethylaminomethyl piperidine hydrochloride

(Example No. 1 of WO 91/17116).

Example 23 of EP-A-333427 shows no evidence of brain 15 penetration by comparing cerebral and plasma levels after subcutaneous administration (1 mg/Kg) of the testing drug.

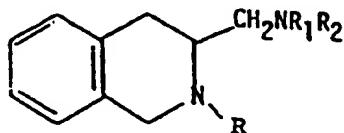
This property, which is in agreement with the very low lipophilicity of the compound [assessed by measuring the $\Delta\log P = \log P(n\text{-octanol}/\text{acq. buffer}) - \log P$

20 (cyclohexane/acq. buffer) = 4.12 at pH=12, 25°C], renders the compound particularly suitable for obtaining a peripherally selective antinociceptive action.

Claims

1. Use of a compound, or a pharmaceutically acceptable
 5 salt or solvate thereof, for the manufacture of a
 medicament for the treatment of inflammation pain,
 wherein the compound is selected from compounds of
 formulae (I), (II), (III), (IV), (V), (VI), (VII),
 (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV) or
 10 (XVI):

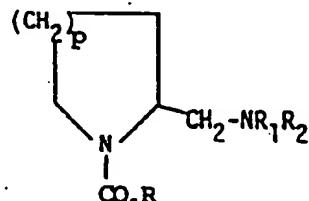
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(I)

20 in which R is an acyl group containing a substituted
 or unsubstituted carbocyclic or heterocyclic aromatic
 ring and R₁ and R₂ are independently C₁₋₆ alkyl groups
 or together form a C₃₋₆ polymethylene or alkenylene
 group;

25

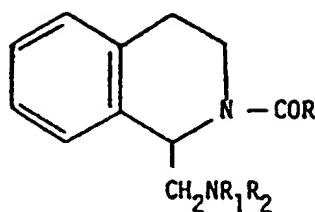


(II)

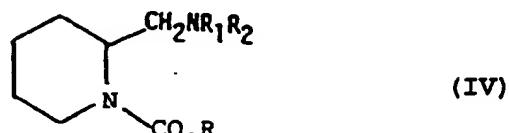
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in which R, R₁ and R₂ are as defined for formula (I),
 and p is 1, 2, 3 or 4;

5



10



15

in which R is a group:

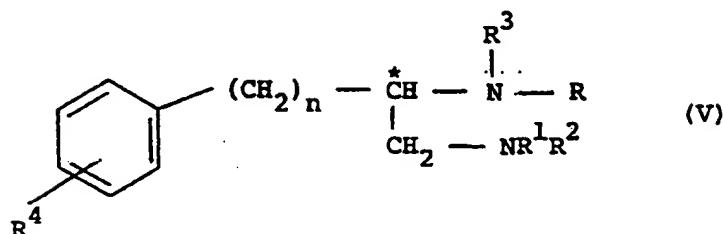
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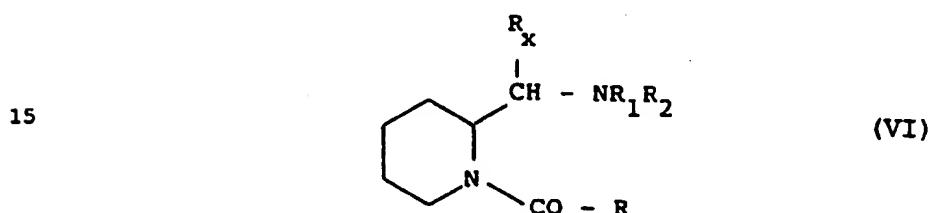
in which R3 is Br, NO2 or CF3; and R1 and R2 are as defined in formula (I);

25

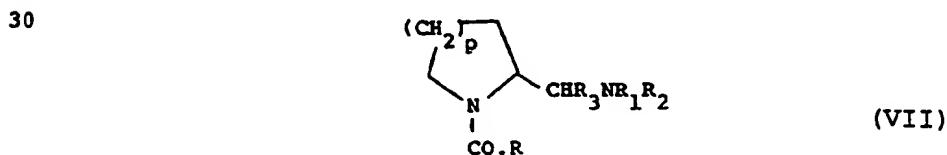
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in which R is as defined in formula (I);
 R¹ and R² each independently represents an alkyl,
 alkenyl or alkynyl group or R¹ together with R²
 5 represents a C₃-6 polymethylene or alkenylene group;
 R³ represents hydrogen or alkyl;
 R⁴ represents hydrogen, halogen, alkyl, hydroxy,
 alkoxy, nitrile, nitro, amino or mono or disubstituted
 amino;
 10 and
 n represents 0 or 1;



in which R is as defined in formula (I);
 20 R₁ and R₂ are independently hydrogen, C₁-6 alkyl, C₂-6 alkenyl, C₄-6 cycloalkyl or C₄-12 cycloalkylalkyl or together form a C₂-6 polymethylene or C₂-6 alkenylene group, optionally substituted with a hetero-atom, provided that R₁ and R₂ are not simultaneously hydrogen;
 25 Rx is C₁-6 alkyl or phenyl, or Rx together with R₁ form a -(CH₂)₃- or -(CH₂)₄- group;



in which R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups, or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group optionally substituted with a hetero-atom, provided that R_1 and R_2 are not simultaneously hydrogen;

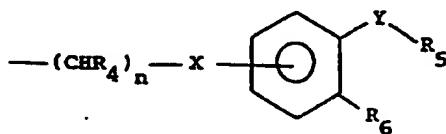
R_3 is hydrogen, C_{1-6} alkyl, or phenyl, or R_3 together

10 with R_1 form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

p is 1, 2, 3 or 4, and

R is a group of formula

15



20 in which the group $-(CH_2)_n-X-$ is in the meta- or para-position with respect to YR_5 or R_6 , R_4 is hydrogen or C_{1-6} alkyl;

n is 0, 1 or 2;

25

X is a direct bond, or O, S or NR_a in which R_a is hydrogen or C_{1-6} alkyl;

Y is $>C=O$, $>CHOH$, $>S=O$ or $>SO_2$;

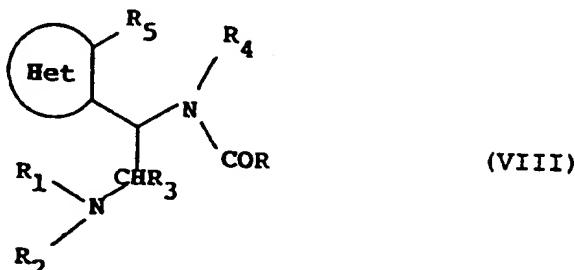
30 each of R_5 and R_6 is C_{1-6} alkyl, or

R_5 and R_6 are linked together and R_5 represents $-(Z)_m-$ where m is 0 or 1 and Z is O, S or NR_7 where R_7 is hydrogen or C_{1-6} alkyl;

and R_6 represents $-(CH_2)_q-$ where q is an integer of from 1 to 4, and in which one or more of the $-(CH_2)-$ groups is optionally substituted by a C_{1-6} alkyl group;

5

10



in which R is as defined in formula (I)

15 R_1 and R_2 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkylalkyl groups or together form a C_{2-8} branched or linear polymethylene or C_{2-6} alkenylene group, optionally substituted with a heteroatom;

20 R_3 is hydrogen, C_{1-6} alkyl, or phenyl or R_3 together with R_1 form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

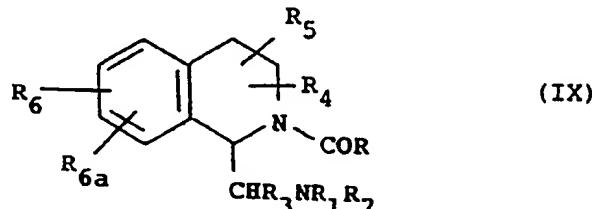
R_4 is C_{1-6} alkyl, or phenyl;

R_5 is hydrogen or together with R_4 forms a $-(CH_2)_n-$ group in which $n = 1, 2$ or 3 ; and

25 'Het' is an optionally substituted single or fused ring heterocyclic group, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur;

30

35



in which R is as defined in formula (I) and R₁ and R₂ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkyl or C₄₋₁₂ cycloalkylalkyl groups or together form a C₂₋₈ branched or linear polymethylene or C₂₋₆ alkenylene group optionally substituted with a hetero-atom;

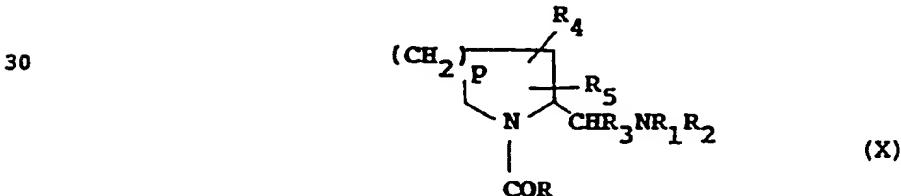
R₃ is hydrogen, C₁₋₆ alkyl, or phenyl or R₃ together with R₁ forms a -(CH₂)₃- or -(CH₂)₄-, group;

R₄ and R₅, which may be the same or different and may be attached to the same or different carbon atoms of the isoquinoline nucleus, are each hydrogen, halogen, hydroxy, C₁₋₆ alkyl, aryl, or R₄ together with R₅ form a -(CH₂)_p group, where p is an integer of from 1 to 5 and one or more of the -(CH₂)- moieties is optionally substituted by a C₁₋₆ alkyl group.

R₆ and R_{6a}, which may be the same or different, are each hydrogen, C₁₋₆ alkyl, -CH₂OR_{6b}, halogen, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, thiol, C₁₋₆ alkylthio,

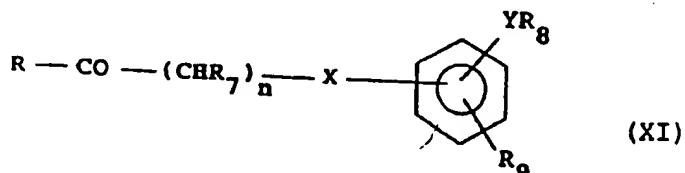
-O-C(=O)-R_{6c}, -NHCOR_{6d}, -NHSO₂R_{6e}, -CH₂SO₂NR_{6f}R_{6g}, in which each of R_{6b} to R_{6g} is independently hydrogen, C₁₋₆ alkyl, aryl or aralkyl;

with the proviso that R₄, R₅, R₆ and R_{6a} are not simultaneously hydrogen;



in which R is as defined in formula (I);
 R₁ and R₂ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkyl or C₄₋₁₂ cycloalkylalkyl groups, or together form a C₂₋₈ branched or linear polymethylene or C₂₋₆ alkenylene group, optionally substituted with a hetero-atom;
 5 R₃ is hydrogen, C₁₋₆ alkyl or phenyl, or R₃ together with R₁ form a -(CH₂)₃- or -(CH₂)₄- group;
 10 R₄ and R₅ are independently hydrogen, hydroxyl, halogen, C₁₋₆ alkyl or aryl, provided both R₄ and R₅ are not simultaneously hydrogen: and p is an integer from 1 to 4;

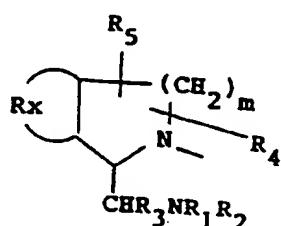
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20

in which R represents a group of formula

25



30

in which R_x is the remainder of a heterocyclic group, or an optionally substituted phenyl group;

R₁ and R₂ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkyl or C₄₋₁₂ cycloalkylalkyl groups, or together form a C₂₋₈ branched or linear polymethylene or C₂₋₆ alkenylene group, optionally substituted with a hetero-atom;

5 R₃ is hydrogen, C₁₋₆ alkyl, or phenyl, or R₃ together with R₁ form a -(CH₂)₃- or -(CH₂)₄- group;

R₄ and R₅, which may be located on the same or different carbon atoms, are independently hydrogen, C₁₋₆ alkyl, or phenyl;

10 m is 1, 2 or 3;

R₇ is hydrogen or C₁₋₆ alkyl;

n is 0, 1 and 2;

X is direct bond, or O, S or NR₆ is hydrogen or C₁₋₆ alkyl;

15 Y is >C=O, >CHOH, >S=O or >SO₂;

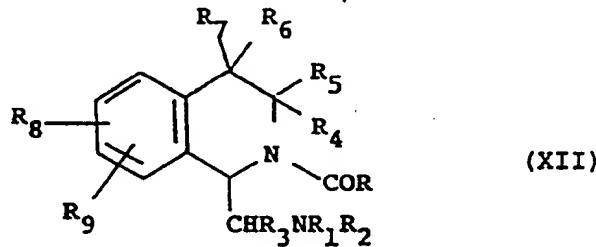
each of R₈ and R₉ is C₁₋₆ alkyl, or

R₈ and R₉ are linked together and R₈ represents -(Z)_p- where p is 0 or 1 and Z is O, S or NR_z where R_z is

20 hydrogen or C₁₋₆ alkyl;

and R₉ represents -(CH₂)_q- where q is an integer of from 1 to 4;

25



30

in which R is as defined in formula (I) and R₁ and R₂ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ cycloalkyl or C₄₋₁₂ cycloalkylalkyl groups or together form a C₂₋₈ branched or linear polymethylene or C₂₋₆ alkenylene group optionally substituted with a hetero-atom;

35

R₃ is hydrogen, C₁₋₆ alkyl, or phenyl, or R₃ together with R₁ forms a -(CH₂)₃- or -(CH₂)₄, group;

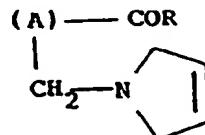
5 R₄ and R₅ are identical and are hydrogen or C₁₋₆ alkyl, or together form a C₂₋₅ linear polymethylene group;

R₆ and R₇ are identical and are hydrogen or C₁₋₆ alkyl, or together form a C₂₋₅ linear polymethylene group;

10 or R₅ and R₆ are together -CH₂- when each of R₄ and R₇ is hydrogen or C₁₋₆ alkyl; with the proviso that R₄, R₅, R₆ and R₇ are not simultaneously hydrogen;

15 R₈ and R₉, which may be the same or different, are each hydrogen, C₁₋₆ alkyl, -CH₂OR₁₀, halogen, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, thiol, C₁₋₆ alkylthio,

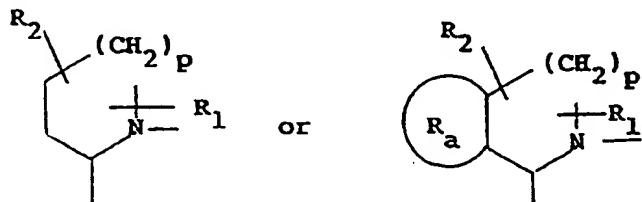
20 -OCR₁₁, -NHCOR₁₂, -NHSO₂R₁₃, -CH₂SO₂NR₁₄R₁₅, in which each of R₁₀ to R₁₅ is independently hydrogen, C₁₋₆ alkyl, aryl or aralkyl;



(XIII)

in which:

(A) is



p is 1, 2 or 3;

ROC- is an acyl group linked to the nitrogen atom of group (A) in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

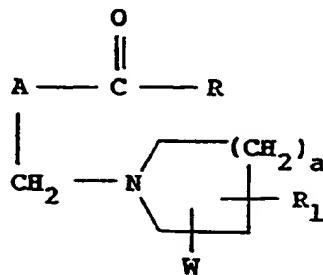
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R₁ and R₂ are substituents on the same or different carbon atoms and are independently hydrogen or C₁₋₆ alkyl;

10

R_a is a fused substituted or unsubstituted heterocyclic or carbocyclic aromatic ring;

15



20

(XIV)

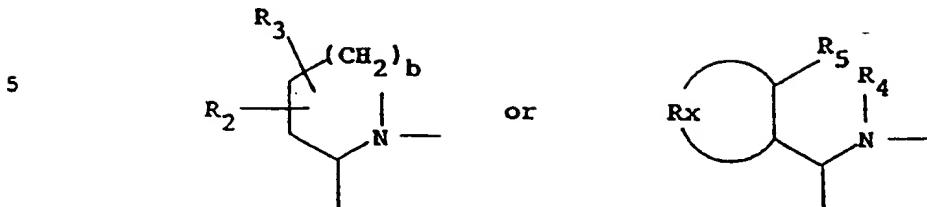
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in which W, which may be attached to the same or different carbon atom as R₁, is hydroxy, C₁₋₆ alkoxy (preferably methoxy), halogen (preferably fluorine), thiol, C₁₋₆ alkylthio, hydroxy C₁₋₆ alkyl, methyldene, hydroxycarbonyl, aminocarbonyl, C₁₋₃ alkoxy carbonyl, NHR_{1a} or NHCOR_{1a} where R_{1a} is H or C₁₋₆ alkyl;

30

R₁ is hydrogen, halogen (preferably fluorine), C₁₋₆ alkyl (preferably methyl) or together with W forms a keto-group or a cyclic ether or thioether containing from 1 to 4 carbon atoms;

A represents



10 in which each of R₂ and R₃, which may be attached to the same or different carbon atom, is hydrogen, C₁₋₆ alkyl, hydroxy, thiol, C₁₋₆ alkoxy, C₁₋₆ alkylthio or halogen (preferably fluorine);

R₄ is C₁₋₆ alkyl;

15 R₅ is hydrogen or together with R₄ forms a -(CH₂)_c- group optionally substituted by one or two C₁₋₆ alkyl groups and attached to the same or different carbon atom;

20 R_x is the remainder of an optionally substituted single or fused ring heterocyclic group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur;

25 or R_x is the remainder of an optionally substituted phenyl group;

a is 1 or 2, b is 1, 2 or 3; c is 1, 2 or 3;

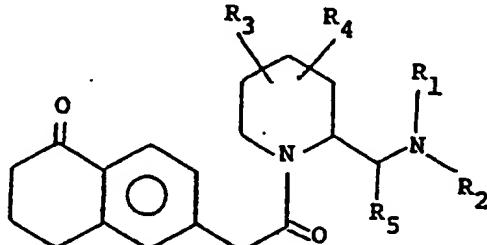
30 and RCO, which is linked to the nitrogen atom of the group A, is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring,

with the provisos that:

- i) When A represents, N-, R represents a tetralon moiety, or W is halogen or C₁₋₆ alkoxy, or R₁ is other than hydrogen or a keto group with W;
- 5 ii) When R₂ is C₁₋₆ alkyl, R₃ is other than hydrogen;
- iii) When R_x, R₄ and R₅ together form an unsubstituted tetrahydroisoquinoline group, R represents a tetralone moiety or R₁ is other than hydrogen or a keto group with W, or W is halogen or C₁₋₆ alkoxy;
- 10 iv) When R_x, R₄ and R₅ together form a substituted tetrahydroisoquinoline group, substitution only occurs in the -(CH₂)_c- group formed by R₄ and R₅;

15

20



(XV)

in which:

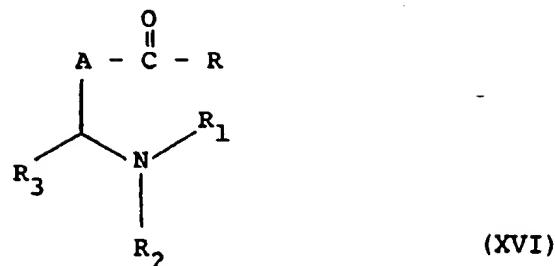
25 R₁ and R₂ are each linear or branched C₁₋₄ alkyl, C₃₋₆ cycloalkyl, C₄₋₆ cycloalkylalkyl, C₃₋₄ alkenyl, C₃₋₆ cycloalkenyl or C₃₋₄ alkynyl;

R₃ and R₄ are identical, and each is hydrogen or C₁₋₄ alkyl; and

30

R₅ is hydrogen or C₁₋₃ alkyl;

5



in which:

10 each of R_1 and R_2 , which may be the same or different, is C_{1-6} alkyl with at least one of them being substituted by at least one of halogen, (preferably fluorine or chlorine), hydroxy, C_{1-6} alkoxy (preferably methoxy), acyloxy (preferably acetoxy),

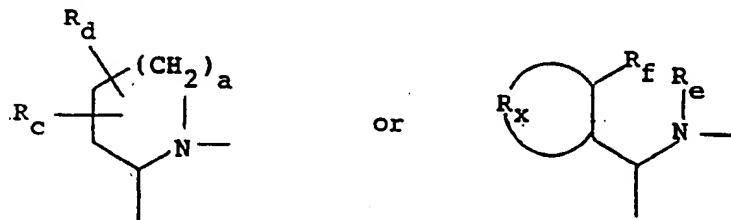
15 thiol, C_{1-6} alkylthio (preferably methylthio), acylthio (preferably acetylthio) halo- C_{1-6} alkoxy (preferably fluoro-alkoxy), COR_h , $COOR_h$, $CONHR_h$ or $NCHOR_h$ where R_h is hydrogen or C_{1-6} alkyl, preferably methyl or ethyl;

20

R_3 is hydrogen or C_{1-3} alkyl, preferably methyl;

A represents

25



30

in which each of R_c and R_d , which may be attached to the same or different carbon atom, is hydrogen, C_{1-6} alkyl, hydroxy, thiol, C_{1-6} alkoxy, C_{1-6} alkylthio or halogen (preferably fluorine);

5 R_e is C_{1-6} alkyl;

10 R_f is hydrogen or together with R_e forms a $-(CH_2)_b-$ group optionally substituted by one or two C_{1-6} alkyl groups and attached to the same or different carbon atom;

15 R_x is the remainder of an optionally substituted single or fused ring heterocyclic group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur; or R_x is the remainder of an optionally substituted or unsubstituted phenyl group;

20 a is 1, 2 or 3; b is 1, 2 or 3;

25 and RCO , which is linked to the nitrogen atom of the group A, is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring.

30 2. A use according to claim 1 in which the compound is selected from:

25 4-(pyrrolidin-1-yl)methyl-5-(3,4-dichlorophenyl)

30 acetyl-4,5,6,7-tetrahydroimidazo [4,5-c] pyridine;

35 (2)-1-(4-trifluoromethyl phenylacetyl)-2-(1-

40 pyrrolidinyl methyl)piperidine;

45 and

50 (2S)-1-[1-oxo-3,4,-dihydro-(2H)-naphth-6-yl]acetyl-2-

55 dimethylaminomethyl piperidine hydrochloride.

60 3. A pharmaceutical composition for use in the treatment of inflammation pain in mammals, which comprises a